Polypharmacy in Elderly Patients with Hypertension

Agarwal N[1], **Agarwal S**[2]✉

1.MS2, St. George's University, Grenada
2.Medical Director, Agarwal Health Center, 52 Richard Road, Edison, NJ 08820 USA

✉**Corresponding author:**
Medical Director, Agarwal Health Center, 52 Richard Road, Edison, NJ 08820 USA,
E-mail: usacardiologist@gmail.com

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ABSTRACT

Polypharmacy is common in the elderly. It continues to increase, despite its known association with increased morbidity and mortality. It increases the risk of inappropriate use of medications, nonadherence, and adverse effects. Patients with polypharmacy also experience a decline in the activities of daily living. It also raises health care costs. Elderly hypertensives are at particular risk for polypharmacy. This stems from the need for multiple anti-hypertensive drugs for proper control of hypertension in this population, complicated by a host of co-morbid conditions such as arthritis, heart disease, cancer, and diabetes mellitus – all requiring concomitant treatment. Health care professionals should be congnizant of the risks of polypharmacy. Physicians need to monitor patient both prescription and non-prescription drug treatment periodically and educate both patients and their families on their proper usage.

Key words: Polypharmacy, Adverse drug effects, Hypertension, Elderly

Abbreviations: ADE - adverse drug effect, BP - Blood pressure, HTN - Hypertension or high blood pressure, OTC - Over the counter medications/supplements

1. INTRODUCTION

The term polypharmacy was first coined in 1959 in the New England Journal of Medicine (Friend, 1959). It is derived from the Greek words polus (many) and pharmakon (drug) and means many drugs. Although polypharmacy has been variously defined, (Berube et al,

1982, Friend, 1959, Sheppard et al, 1969, Fulton et al, 2005, Frazier, 2005, Zarowitz et al, 2005, Brager et al, 2005) it is commonly referred to the concomitant use of multiple medications, usually five or more drugs, (Bjerrum et al, 1997, Kennerfalk, 2002) and/or the use of inappropriate medications (Raji et al, 2003). Other definitions include the use of more drugs than are clinically indicated, (Zarowitz et al, 2005) or the use of two or more medications to treat the same condition, (Faries et al, 2005) and the use of two or more drugs of the same chemical class (Brager et al, 2005). It is often confounded by the patient's use of over the counter drugs, herbal remedies, and foods or nutraceuticals for self medication, with potentially interacting with prescribed medications. The objective of this office based study was to study the epidemiology of polypharmacy in elderly hypertensives and to briefly review controlled studies designed to reduce polypharmacy in the elderly.

2. METHODS

We reviewed the medical records of 100 consecutive hypertensive patients over the age of 65 seen in our office. The total numbers of medications, irrespective of the prescribing source, were counted. Hypertension was diagnosed according to JNC 7 (JNC 7 Report, 2003). The categories are based on the average of 2 or more seated BP measurements on 2 separate occasions, Normal, less than 120/80 mmHg, Pre-HTN, 120 to 139/80 to 89 mmHg, HTN, 140/90 mmHg or greater, Stage 1, 140 to 159/90 to 99 mmHg, Stage 2, 160/100 mmHg or greater. BP greater than 130/80 mmHg in patients with diabetes mellitus or renal disease was regarded as HTN. All patients were under treatment for hypertension according to the guidelines (Chobanian, 2003). BP goal was less than 130/80 mmHg in patients with renal disease, and less than 140/90 mmHg in all other patients (Moser, 2004).

3. RESULTS

Of the 100 consecutive hypertensive patients under treatment, there were 48 males and 52 females (Figure 1). Chart, medication bottles and pharmacy printout reviews revealed, none (0%) of the patients were on 1 or 2 medications, 4 (4%) were on 3, 4 (4%) were on 4, 12 (12%) were on 5, 16 (16%) were on 6, 12 (12%) were on 7, 18 (18%) were on 8, 14 (14%) were on 9 and 20 (20%) were on 10 medications or more. Only 8% were on less than 5 medications. 92% were on 5 or more, 52% were on 8 or more and 20% on 10 or more medications. OTC medications and herbal supplements were not tabulated in this study. There were no differences of any significance between the sexes.

4. DISCUSSION

Polypharmacy is a worldwide phenomenon (van der Hooft et al, 2005, Lai HY et al, 2009, Ryan C et al, 2009) and is especially common in the elderly patients (Hajjar ER et al, 2007, Fulton, 2005). Elderly patients suffer from chronic diseases and have complicated pathology, making them more likely to experience polypharmacy. Polypharmacy in these patients is therefore usually medically indicated and appropriate (Preskorn, 2005). Gurwitz reported that more than 90 percent of people 65 or older use at least 1 medication per week, more than 40 percent of this population use 5 or more different medications per week, and 12 percent use 10 or more different medications per week (Gurwitz, 2004). In one study of 28,000 patients aged 65 or more, investigators found that 75 percent of the sample received prescriptions for 6 or more prescription drugs, (Gurwitz et al, 2003). The most common medications were, cardiovascular (53.2%), antibiotics/anti-infectives (44.5%), diuretics (29.5%), opioids (21.9%), anti-hyperlipidemic (21.7%), non-opioid analgesics (19.8%), gastrointestinal tract (19.0%), respiratory tract (15.6%), dermatologic (14.8%), antidepressants (13.2%), sedatives/hypnotics (12.9%), and nutrients/supplements (12.3%). Polypharmacy is even more rampant in the hospitalized elderly. In one study of patients hospitalized from home care agencies, 66% used five or more drugs, 46% used more than seven drugs and 21% used 10 or more drugs (Flaherty 2000). It is estimated that ten percent of the general population regularly takes over the counter (OTC) or non-prescription medications (Memmott, 2003, Salom, 1995). OTC medication use is also quite prevalent in the elderly - 40 percent of the drugs taken by the elderly are OTC drugs. It has been estimated that 69% of the people over the age of 65 use OTC medications, with almost 20 percent withholding this information from their physicians. Pain, cough and cold medications are the most common OTC medications consumed. Vitamins, minerals, antacids and laxatives are also commonly obtained without a prescription (Stoehr et al, 1997). Elderly patients also often combine alcohol use with medication intake – another factor potentially aggravating the detrimental effects of polypharmacy (Memmott, 2003, Salom, 1995).

5. CAUSES OF POLYPHARMACY

Co-morbidity is a major cause of polypharmacy in the elderly population (Buckley et al, 2001, Geest et al, 2004). Poor health and diseases such as hypertension, diabetes mellitus, asthma, arthritis, depression, diverticulosis and anemia increase the risk of polypharmacy (Chrischilles et al, 1992). Multiple health care providers and an increased number of health care visits also increases the

risk and the associated morbidity (Jorgensen et al, 2001, Green et al, 2007). White race, increased age, low education and income, and unsubstantiated health-related beliefs, also play a critical role with unnecessary drug use in the elderly (Hanlon et al, 1992, Rossi et al, 2007). Polypharmacy is even more alarmingly high in the elderly in institutions (Liu et al, 2002). Mental illness is another prominent cause for polypharmacy (Tani et al, 2012, Sheppard et al, 1969). The primary psychiatric reason for multiple drug use is to gain rapid therapeutic response as well as to bolster medication effectiveness in treating patients with refractory psychotic and mood symptoms, or behavioral problems. Unfortunately, it increases morbidity and mortality in these patients (Tiihonen et al, 2012).

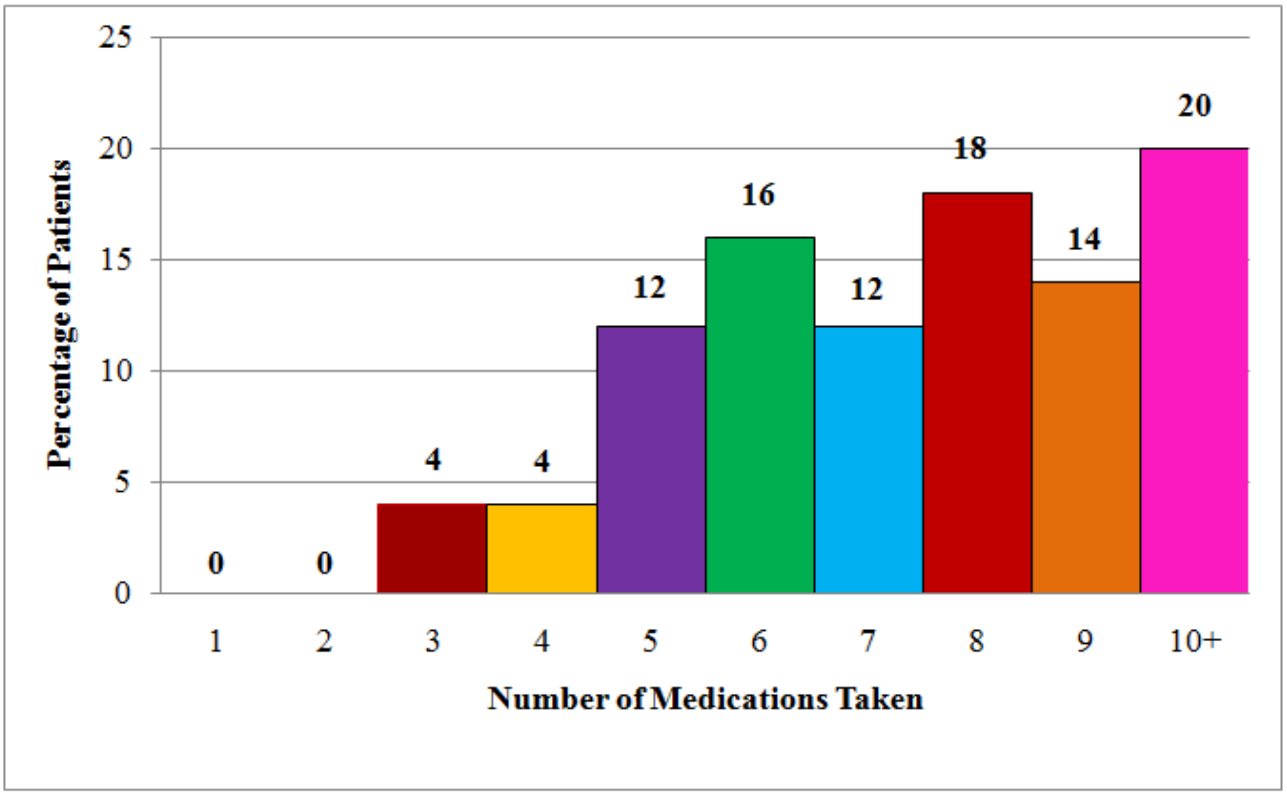

Figure 1
Chart for 100 consecutive hypertensive patients under treatment

6. POLYPHARMACY AND ASSOCIATED ADVERSE EFFECTS

Polypharmacy is associated with an increased incidence of adverse events (Calderón-Larrañaga et al, 2012) and a higher mortality (Espino et al, 2006). Polypharmacy is associated with a decline in physical and instrumental activities of daily living (Magaziner et al, 1989). The concomitant intake of a psychotropic drug in the older population greatly increases the risk of hip fracture (Ray et al, 1987) and automobile accidents (Ray et al, 1992). In a major study, investigators (Gurwitz, et al, 2003) found that the most common adverse reactions occurred with the following drug groups, cardiovascular medications (24.5% of the ADEs) diuretics (22.1% of the ADEs), non-opioid analgesics (15.4% of the ADEs), hypoglycemics (10.9% of the ADEs) and anticoagulants (10.2% of the ADEs). Col and associates found that adverse events or non-adherence to drug therapy was responsible for 28% of older patients' hospitalizations (Col et a, 1990). Re-hospitalizations within 6 months are seen in 35% of older patients taking three or more prescription medications at hospital discharge and 6.4% of these involve medication related problems (Bero et al. 1991). Studies suggest that approximately 40% of elderly patients are taking more than five prescribed medications.

Taking five or more drugs increases medication-related adverse effects such as cognitive dysfunction, frailty, depression, incontinence and falls in the elderly (Gnjidic et al, 2012, LeRoy, 2004). There is an increase in drug to drug interactions and side effects may confound the effects of one another. Side effects with one medication may also create the need for more medication, increasing the pill burden. A high pill burden further increases the possibility of non-compliance or mal-compliance. Several studies have concluded that drug metabolism may be diminished in the elderly, making them more prone to ADEs (Schmucker, 2001, Kinirons et al, 2004). Polypharmacy has been associated with increased hospitalizations, medication errors, and increased health care costs. The elderly

disproportionately comprise the expenditure on medications compared to the rest of the population (Linjakumpu et al, 2002, Herrlinger, et al, 2001). According to data released in 2005, hospital admissions related to adverse events from medications in older patients cost $20 billion annually in the US (excluding indirect costs), (Publication AO/HEHS, 1995) while morbidity and mortality related to drug therapy in ambulatory patients cost $76.6 billion annually (Johnson et al, 1995). The US Center for Medicare and Medicaid Services estimated in 2002 that polypharmacy costs its nation's health plans more than US$50 billion annually (Berenbeim et al, 2002). Total costs today are probably much higher. Finally, a high pill burden is a source of non-compliance and dissatisfaction for many patients.

7. POLYPHARMACY PREVENTION

Serious problems associated with polypharmacy are coming under increasing scrutiny (Dovjak et al, 2012) and attempts to devise and implement tools to decrease this dangerous trend are being studied (Patterson et al, 2012). Immediate and critical interventions are needed to stem this growing trend towards polypharmacy (Kaur et al, 2009). Physicians may be able to resort to non-pharmacologic therapy, including diet modification or exercise, instead of medication in some patients. Drug utilization review tools in pharmacies can signal potentially inappropriate prescribing due to excessive or suboptimal dosage or duration, therapeutic duplication or drug to drug interaction (Castelino et al, 2009). Increasing drug surveillance and restricting similarly working medications by insurance companies can greatly reduce excessive and inappropriate polypharmacy. In hospitals and institutions, computerized pharmacy and nursing programs can help stem polypharmacy by flagging drugs to avoid, drugs that should be limited in dose or duration, drugs to be monitored, and drug-drug interactions (Aspinall et al, 2007). Office based physicians also need to set targeted therapeutic goals when prescribing medications. Real time e-prescribing and assessing medication regimens on a regular basis will also help in reducing inappropriate polypharmacy. Finally, once or twice a day drug schedule and medication education for both patients and their families can improve compliance and inappropriate intake (Cramer, 1998).

8. CONCLUSION

Polypharmacy is common in elderly hypertensives. The vast majority of our patients were on five or more prescribed medications. Besides being on an average of four anti-hypertensives, most patients were also on one anti-arthritis, anti-cholesterol, anti-platelet and anti-anxiety/and insomnia medication. Although extremely common, polypharmacy in this population may be unavoidable due to the presence of several concomitant medical conditions. The potential of adverse clinical outcomes however exist, despite a justifiable use. Further, physicians should remain cognizant of the fact that a large number of these patients may also be on OTC medications, which can further confound the issue.

SUMMARY OF RESEARCH

Our study finds that the vast majority of elderly hypertensives are on more than 5 medications. In most cases, blood pressure control itself required four or more different medications from different antihypertensive drug classes. Although this polypharmacy is justifiable and also more extreme due to the presence of many other co-existing morbid conditions in this population, the health dangers attributable to multiple medication use remain. Physicians should be extremely cognizant of the potentially dangerous situation involving polypharmacy in this group. Rigorous drug monitoring and a constant vigilance for adverse reactions from multiple medication use are needed, especially in the elderly hypertensive.

FUTURE ISSUES

More research is required to further delineate the consequences associated with multiple drug use in elderly patients. Properly designed prevention and intervention studies are also needed to devise strategies to reduce polypharmacy in this population.

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Data and materials availability: All data associated with this study are present in the paper.

REFERENCE

1. Aspinall S, Sevick MA, Donohue J, Maher R, Hanlon JT. Medication errors in older adults, a review of recent publications. *Am J Geriatr Pharmacother*. 2007, 5(1), 75-84
2. Berenbeim DM. Polypharmacy: overdosing on good intentions. *Manag Care Q*. 2002, 10(3), 1-5
3. Bero LA, Lipton HL, Bird JA. Characterization of geriatric drug-related hospital readmissions. *Med Care* 1991, 29(10), 989–1003
4. Berube MS, Neely DJ, DeVinne PB. American Heritage Dictionary. (2nd College ed). Boston, Houghton Mifflin Co, 1982
5. Bjerrum L, Rosholm JU, Hallas J, Kragstrup J. Methods for estimating the occurrence of polypharmacy by means of a prescription database. *Eur J Clin Pharmacol* 1997, 53(1), 7–11
6. Brager R, Sloand E. The spectrum of polypharmacy. *Nurse Pract*. 2005, 30, 44–50
7. Buckley BM. Healthy ageing: ageing safely. *Eur Heart J*. 2001, 3(Suppl. N), N6–10
8. Calderón-Larrañaga A, Poblador-Plou B, González-Rubio F, Gimeno-Feliu LA, Abad-Díez JM, Prados-Torres A. Multimorbidity, polypharmacy, referrals, and adverse drug events: are we doing things well? *Br J Gen Pract*. 2012, 62(605), 821-6
9. Castelino RL, Bajorek BV, Chen TF. Targeting suboptimal prescribing in the elderly: a review of the impact of pharmacy services. *Ann Pharmacother*. 2009, 43(6), 1096-106
10. Chobanian AV, Bakris GL, Black HR. National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. 2004, 42(6), 1206-52
11. Chrischilles EA, Foley DJ, Wallace RB. Use of medications by persons 65 and over, Data from the established populations for epidemiologic studies of the elderly. *J Gerontol*. 1992, 47, M137-M144
12. Col N, Fanale JE, Kronholm P. The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly. *Arch Intern Med*, 1990, 150(4), 841–5
13. Cramer JA. Enhancing patient compliance in the elderly. Role of packaging aids and monitoring. *Drugs and Aging*. 1998, 12, 7-15
14. Dovjak P. Tools in polypharmacy. Current evidence from observational and controlled studies. The problem of polypharmacy is under serious scrutiny. *Z Gerontol Geriatr*. 2012, 45(6), 468-72
15. Espino DV, Bazaldua OV, Palmer RF. Suboptimal medication use and mortality in an older adult community- based cohort, Results from the Hispanic EPESE Study. *J Gerontol A Biol Sci Med Sci*. 2006, 61, 170-175
16. Faries D, Ascher-Svanum H, Zhu B, Correll C, Kane J. Antipsychotic monotherapy and polypharmacy in the naturalistic treatment of schizophrenia with atypical antipsychotics. *BMC Psychiatry*. 2005, 5, 26
17. Flaherty JH, Perry HM, III, Lynchard GS, Morley JE. Polypharmacy and hospitalization among older home care patients. *J Gerontol A Biol Sci Med Sci*. 2000, 55, M554–M559
18. Fleischhacker WW, Uchida H. Critical review of antipsychotic polypharmacy in the treatment of schizophrenia. *Int J Neuropsychopharmacol*. 2012, 1-11
19. Frazier SC. Health outcomes and polypharmacy in elderly individuals: an integrated literature review. *J Gerontol Nurs*. 2005, 31, 4–11
20. Friend DG. Polypharmacy: multiple-ingredient and shotgun prescriptions. *N Engl J Med* 1959, 260(20), 1015–8
21. Fulton MM, Allen ER. Polypharmacy in the elderly: a literature review. *J Am Acad Nurse Pract*.2005, 17, 123–32
22. Geest SD, Steeman E, Leventhal ME, Mahrer-Imhof R, Hengartner-Kopp B, Conca A, Bernasconi AT, Petry H, Rocca HB-L. Complexity in caring for an ageing heart failure population, concomitant chronic conditions and age related impairments. *Eur J Cardiovasc Nurs*. 2004, 3, 263–70
23. Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Waite L,t al. Polypharmacy cutoff and outcomes, five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. *J Clin Epidemiol*. 2012 Sep, 65(9), 989-95
24. Green JL, Hawley JN, Rask KJ. Is the number of prescribing physicians an independent risk factor for adverse drug events in an elderly outpatient population? *Am J Geriatr Pharmacother*. 2007 Mar, 5(1), 31-9
25. Gurwitz JH, Field TS, Harrold LR, Rothschild J, Debellis K, Seger AC, Cadoret C, Fish LS, Garber L, Kelleher M, Bates DW. Incidence and preventability of Adverse Drug Events Among Older Persons in the Ambulatory Setting. *Journal of the American Medical Association*, 2003, 289(9), 1107-1116
26. Gurwitz JH. Polypharmacy: A New Paradigm or Quality Drug Therapy in the Elderly?" Archives of Internal Medicine, 2004, 164, 18, 1957-1959
27. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. *Am J Geriatr Pharmacother*. 2007 Dec, 5(4), 345-51
28. Hanlon JT, Fillenbaum GG, Burchett B. Drug-use patterns among black and nonblack community-dwelling elderly. *Ann Pbarmacotber*. 1992, 26, 679-685
29. Herrlinger C, Klotz U. Drug Metabolism and Drug Interactions in the Elderly. *Best Practice & Research Clinical Gastroenterology*, 2001, 15, 897-918

30. JNC 7 Report, Aram V. Chobanian, MD, George L. Bakris, MD,et al and the National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *JAMA*. 2003, 289(19), 2560-2571
31. Johnson JA, Bootman JL. Drug-related morbidity and mortality. A cost-of-illness model. *Arch Intern Med* 1995, 155(18), 1949–56
32. Jorgensen T, Johansson S, Kennerfalk A. Prescription drug use, diagnoses, and healthcare utilization among the elderly. *Ann Pharmacother*. 2001, 35, 1004-1009
33. Kaur S, Mitchell G, Vitetta L, Roberts MS Interventions that can reduce inappropriate prescribing in the elderly, a systematic review. *Drugs and Aging*. 2009, 26(12), 1013-28
34. Kennerfalk A, Ruigómez A, Wallander M, Wilhelmsen L, Johansson S. Geriatric Drug Therapy and healthcare Utilization in the United Kingdom. *The Annals of Pharmacotherapy*, 2002, 36, 797-803
35. Kinirons MT, O'Mahony MS. Drug Metabolism and Ageing. *Br. J. Clin. Pharmacol*. 2004, 57, 540-544
36. Lai HY, Hwang SJ, Chen YC, Chen TJ, Lin MH, Chen LK. Prevalence of the prescribing of potentially inappropriate medications at ambulatory care visits by elderly patients covered by the Taiwanese National Health Insurance program. *Clin Ther*. 2009, 31(8), 1859-70
37. LeRoy A. Draft Report: Exploratory Study of the Relationship Between Multiple Medicines and Vehicle Crashes—Analysis of Databases. Unpublished manuscript, IATROGEN, Herndon, VA
38. Linjakumpu T, Hartikainen S, Klaukka T, Kivelä S, Isoaho R. Psychotropics Among the Home-Dwelling Elderly—Increasing Trends. *Journal of Geriatric Psychiatry*, 2002, 17, 874-883
39. Liu GG, Christensen DB. The continuing challenge of inappropriate prescribing in the elderly: an update of the evidence. *J Am Pharm Assoc (Wash)*. 2002, 42(6), 847-57
40. Magaziner J, Cadigan DA, Fedder DO, Hebel JR. Medication use and functional decline among community dwelling older women. *J Aging Health*. 1989, 1, 470- 484
41. Memmott JL. Social Work Practices with the Elderly Substance Abuser. *Journal of Social Work Practice in the Addictions*, 2003, 3(2), 85-103
42. Moser M. Update on the management of hypertension: recent clinical trials and the JNC 7. *J Clin Hypertens (Greenwich)*. 2004, 6(10 Suppl 2), 4-13
43. Patterson SM, Hughes C, Kerse N, Cardwell CR, Bradley MC. Interventions to improve the appropriate use of polypharmacy for older people. *Cochrane Database Syst Rev*. 2012, 5, CD008165
44. Prescription drugs and the elderly. Publication AO/HEHS-95-152.Washington, DC: U.S. General Accounting Office, July 1995
45. Preskorn SH. Multiple medication use in patients seen in the Veterans Affairs healthcare system: So what? *J Psychiatr Pract*. 2005, 11, 46–9
46. Raji MA, Ostir GV, Markides KS, Espino DV, Goodwin JS. Potentially Inappropriate Medication Use by Elderly Mexican Americans. *The Annals of Pharmacotherapy*, 2003, 37, 1197-1202
47. Ray WA, Fought RL, Decker MD. Psychoactive drugs and the risk of injurious motor vehicle crashes in elderly drivers. *Am J Epidemiol* 1992, 136(7), 873–83
48. Ray WA, Griffin MR, Schaffner W, Baugh DK, Melton LJ 3rd. Psychotropic drug use and the risk of hip fracture. *N Engl J Med* 1987, 316(7), 363–9
49. Rossi MI, Young A, Maher R, Rodriguez KL, Appelt CJ, Perera S, Hajjar ER, Hanlon JT. Polypharmacy and health beliefs in older outpatients. *Am J Geriatr Pharmacother*. 2007, 5(4), 317-23
50. Ryan C, O'Mahony D, Kennedy J, Weedle P, Byrne S. Potentially inappropriate prescribing in an Irish elderly population in primary care. *Br J Clin Pharmacol*. 2009, 68(6), 936-47
51. Salom IL, Davis K. Prescribing for Older Patients: How to Avoid Toxic Drug Interactions. *Geriatrics*, 1995, 50(10), 37-45
52. Schmucker DL. Liver Function and Phase I Drug Metabolism in the Elderly: A Paradox. *Drugs and Aging* 2001, 18, 837-851
53. Sheppard C, Collins L, Fiorentino D, Fracchia J, Merlis S. Polypharmacy in psychiatric treatment. I. Incidence at a state hospital. *Curr Ther Res Clin Exp* 1969, (12), 765–74
54. Stoehr GP, Ganguli M, Seaberg EC. Over-the- counter medication use in an older rural community: The MOVIES Project. *J Am Geriatr Soc.* 1997, 45, 158-165
55. Tani H, Uchida H, Suzuki T, Fujii Y, Mimura M. Interventions to reduce antipsychotic polypharmacy: A systematic review. *Schizophr Res*. 2012
56. Tiihonen J, Suokas JT, Suvisaari JM, Haukka J, Korhonen P. Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. *Arch Gen Psychiatry*. 2012, 69(5), 476-83
57. van der Hooft CS, Jong GW, Dieleman JP, Verhamme KM, van der Cammen TJ, Stricker BH, Sturkenboom MC. Inappropriate drug prescribing in older adults, the updated 2002 Beers criteria - a population-based cohort study. *Br J Clin Pharmacol*. 2005, 60(2), 137-44
58. Zarowitz BJ, Stebelsky LA, Muma BK, Romain TM, Peterson EL. Reduction of high-risk polypharmacy drug combinations in patients in a managed care setting. *Pharmacotherapy*. 2005, 25, 1636–45